Alpha- and beta-adrenergic stimulation of human myometrial activity in-vitro and synthesis of prostaglandins (PG E2,PG F2a,6-keto-PGF1a)

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Beta-adrenergic stimulants inhibit spontaneous and induced uterine contractions. Despite numerous clinical and experimental data the mechanism of their action is still uncertain. Possible factors are the activation of adenylate cyclase reducing myosin light chain phosphorylation and intracellular calcium concentrations, their influence on the system of ion transport and the oxytocin-oxytocinase system. Since in the regulation of uterine motor activity prostaglandins play a basic role it is also conceivable that the effect of beta-adrenergic agonists takes place by modulating the synthesis of prostaglandins. In our investigations the effects of adrenaline and different alpha- and beta-adrenergic agonists and antagonists on the mechanical activity and prostaglandin biosynthesis in the pregnant human myometrium in-vitro were determined.

Pregnant human myometrial samples were excised from the edge of surgical incision in cesarean sections. The myometrial strips (n=23) were superfused with oxygenated tyrode solution and fractionated in 5 min. intervals. The medium was analyzed for prostaglandin E 2, prostaglandin F 2 a, 6-keto-prostaglandin F 1 a by specific radioimmunoassays.

In the first series of investigations the effect of adrenaline and noradrenaline on the spontaneous activity of pregnant human myometrial strips were compared. Both adrenaline and noradrenaline stimulated the myometrium to contract (1o ng/ml, 1oo ng/ml, 1 µg/ml). The dose dependent stimulation of the uterine activity correlated with increasing prostaglandin synthesis of the myometrium strips. Compared to the basal concentrations during spontaneous activity there was a highly significant increase of PG E 2 > PG F 2 a > 6-keto PG F 1 a during adrenergic stimulation (table).

In further studies the influence of alpha- and beta-adrenergic antagonists on the adrenaline effect was investigated. The stimulating effect of adrenaline could be inhibited by specific alpha-blocking substances like phentolamin, prazosine and yohimbine. This inhibition of the alpha-adrenergic activity of adrenaline was associated with low levels of PG F 2 a and PG E 2 comparable to those concentrations that were measured without adrenaline stimulation. Coinciding with the now reduced and inhibiting adrenaline effect an increase of 6-keto-PG F 1 a formation was measured (table). Orciprenaline a beta-stimulating agent had the same effect. It inhibited the synthesis of PG F 2 a and PG E 2 and the stimulation of prostacyclin synthesis was the most expressed.

Superfusion of the myometrium strips with adrenaline together with the beta-adrenergic antagonist pindolole had a strong contractions stimulating effect and resulted in an increase of the PG E 2 and PG F 2 a and a decrease of 6-keto-PG F 1 a synthesis. This effect was even more pronounced by using norfenephrine a specific alpha-adrenergic agonist with a marked stimulatory effect on PG E 2 and PG F 2 a synthesis.

The results demonstrate the dependency of human myometrial activity on alpha- and beta-adrenergic stimulation. Stimulation of alpha-receptors is responded by increased PG E 2 and PG F 2 a synthesis. Stimulation of beta-receptors corresponds with relaxation and enhanced 6-keto-PG F 1 a formation. It is therefore concluded that betamimetics are effective uterine relaxants by stimulating prostacyclin synthesis.

Table: Effect of alpha- and beta-adrenergic stimulation on PG - synthesis in isolated gestational human myometrial strips

	PG F 2 a	PG E 2	6-keto PG F 1 a
SPONTANEOUS ACTIVITY	0.39±0.17	2.46±1.26	1.90±0.37
ADRENALINE 1 µg/ml	1.83±0.21*	13.73±2.95*	5.77±0.94*
ADRENALINE 1 µg/ml PRAZOSINE 1 µg/ml	0.42±0.27	3.24±1.31	6.36±0.22*
ADRENALINE 1 µg/ml YOHIMBINE 1 µg/ml	0.36±0.16	3.42±1.52	10.51±1.81*
ADRENALINE 1 µg/ml PINDOLOLE 1 µg/ml	10.84+1.93*	20.28±0.91*	5.74±1.06
ORCIPRENALINE 1o ng/ml	0.31±0.22	2.13±0.20	7.02±0.81*
NORFENEPHRINE 5o ng/ml	18.72±1.85*	33.19±2.60*	3.41±0.11

Prostaglandin-concentration in ng/ml/g wet weight, ± = SD,

* = $p < 0.05$